

The effects of the national vaccination program and massive migration on the epidemiology of hepatitis A in children from 2013 to 2018

Ulusal aşı programı ve kitlesel göçün, 2013-2018 arasında çocuklarda hepatit A epidemiyolojisine etkileri

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ABSTRACT

Aim: Acute hepatitis A is a common public health problem in underdeveloped and developing countries. The hepatitis A vaccine was implemented as part of the National Immunization Program in Turkey in November 2012. The present study aimed to investigate the effects of the national vaccination program and massive migration on the epidemiology and clinical burden of hepatitis A infection.

Material and Method: The study was a single center, retrospective chart review study among children diagnosed with viral hepatitis A infection between 0 and 18 years of age from January 2013 to February 2018 in Gaziantep Cengiz Gökçek Maternity and Children Hospital, Turkey. All cases' age, diagnosis time, nationality, and gender information were evaluated. The length of stay, the maximum value of alanine transaminase and aspartate aminotransferase, and the direct medical cost of hospitalization were also evaluated in hospitalized cases.

Results: During the study period total of 1039 cases were diagnosed with hepatitis A infection. Of these cases, 53% were males, 14% were Syrian refugees, and the median age was 7.9-year. The number of cases per year (2013 through 2017) was 321, 360, 157, 119, and 73, respectively. The majority of the cases were detected in November, December, and January. While the total number of cases was declining, we saw that the number of Syrian cases was increasing. The percentage of Syrian children in total cases in 2013 and 2017 was 6.5% and 52.1%, respectively. The hospitalization rate was %49.4, the median length of stay was four days, and the average medical cost of hospitalization was 246.8\$/case.

Conclusion: With the national vaccination program, prevalence is declining, but the number of susceptible individuals in society is still adversely affecting the epidemiology of the disease. Continuous monitoring of epidemiological data and efforts to expand vaccine coverage are required for infection control.

Keywords: Hepatitis A, vaccine, pediatric, epidemiology, migration

ÖZ

Amaç: Akut hepatit A, az gelişmiş ve gelişmekte olan ülkelerde yaygın olarak görülen bir halk sağlığı sorunudur. Hepatit A aşısı, Kasım 2012'de Türkiye'de Ulusal Bağışıklama Programının bir parçası olarak uygulanmaya başlanmıştır. Bu çalışma, ulusal aşılama programının ve kitlesel göçün hepatit A enfeksiyonunun epidemiyolojisi ve klinik yükü üzerindeki etkilerini araştırmayı amaçlamıştır.

Gereç ve Yöntem: Çalışma, Cengiz Gökçek Kadın Doğum ve Çocuk Hastanesi, Türkiye'de Ocak 2013 ile Şubat 2018 arasında 0-18 yaş arasında viral hepatit A enfeksiyonu tanısı alan çocuklar arasında tek merkezli, geriye dönük yapılmıştır. Tüm olguların yaş, tanı zamanı, uyruk ve cinsiyet bilgileri değerlendirildi. Hastanede yatan vakalarda kalış süresi, alanin transaminaz ve aspartat aminotransferazın maksimum değerleri ve hastaneye yatışın doğrudan tıbbi maliyeti de değerlendirildi.

Bulgular: Çalışma süresince toplam 1039 vakaya hepatit A enfeksiyonu tanısı konuldu. Bu vakaların %53'ü erkek, %14'ü Suriyeli mülteci ve ortalama yaş 7,9 yıldır. Yılda (2013-2017) vaka sayısı sırasıyla 321, 360, 157, 119 ve 73 idi. Vakaların çoğu Kasım, Aralık ve Ocak aylarında tespit edildi. Yıllar içerisinde toplam vaka sayısı azalırken, Suriyeli vaka sayısının arttığını gördük. 2013 ve 2017 yıllarında toplam vakalarda Suriyeli çocukların oranı sırasıyla %6,5 ve %52,1'dir. Hastanede yatış oranı %49,4, medyan kalış süresi dört gün ve ortalama hastanede yatış maliyeti 246,8\$/vaka idi.

Sonuç: Ulusal aşılama programı ile prevalans azalmaktadır ancak toplumdaki duyarlı birey sayısı halen hastalığın epidemiyolojisini olumsuz etkilemektedir. Enfeksiyon kontrolü için epidemiyolojik verilerin sürekli izlenmesi ve aşı kapsamını genişletme çabaları gereklidir.

Anahtar Kelimeler: Hepatit A, aşı, pediatrik, epidemiyoloji, göç

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INTRODUCTION

Hepatitis A virus (HAV) is an important and common cause of viral hepatitis worldwide, with significant differences in geographical endemicity and clinical characteristics (1-3). The severity and clinical course of the infection vary according to the patient's age. When acquired in the early years of life, HAV infection is often asymptomatic. With advancing age, jaundice and other symptoms usually occur; liver failure and death are possible complications, though they rarely occur. Turkey added the HAV vaccine to its routine immunization schedule at the end of 2012. Studies conducted in different parts of Turkey revealed that the hepatitis A seroprevalence varied by region and time (4).

On the one hand, the introduction of the HAV vaccine into the routine national vaccination plan, on the other hand, the mass migration to Turkey due to the war in Syria were the factors that directly affected the epidemiology of HAV infection. Many factors such as the lack of routine HAV vaccination in Syria, the disruptions in the follow-up of childhood vaccinations during mass migration, the lifestyle in crowded conditions, and the lack of attention to adequate sanitation increased the number of individuals susceptible to HAV infection among the immigrants and indirectly in the whole population (5). The present study aimed to investigate the effects of the national vaccination program and massive migration on the epidemiology and clinical burden of HAV infection.

MATERIAL AND METHOD

All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The study was carried out with the permission of Firat University, Non-Interventional Research Ethics Committee (Date: 19.04.2018, Decision No: 08/16). With the ethics committee approval, the data were reviewed retrospectively using the Hospital Information Management System.

The study was conducted as a single center, retrospective chart review study. Children between 0 and 18 years of age diagnosed with HAV infection from January 2013 to February 2018 in Gaziantep Cengiz Gökçek Maternity and Children Hospital were evaluated. The diagnosis of acute viral hepatitis A was made with HAV immunoglobulin M (IgM) positivity. Demographic features (age, gender, nationality, and diagnosis time) were recorded in all patients. In the second part of the study, hospitalizations due to HAV infection were evaluated in detail. The length of stay (LOS), the maximum value of alanine transaminase (ALT) and aspartate aminotransferase (AST) during the hospitalization, and the direct medical costs (including only hospital expenses) were analyzed in hospitalized patients.

Statistical Analysis

The statistical data analysis was performed using IBM SPSS for Windows (IBM statistics for Windows version 25, IBM Corporation, Armonk, New York, United States). In descriptive statistics of the data, mean $\pm$ standart deviation for normally distributed variables and median (min-max) values for non-normally distributed variables were used. The qualitative data were analyzed by chi-square test, while the quantitative data by Student's t-test or Mann-Whitney test, as appropriate. $P<0.05$ was accepted as a cutoff value for statistical significance.

RESULTS

The total number of HAV IgM tests performed during the study period was 17469. The number of positive results was 1137 (6.5%). When repeated tests of the same person are excluded, 1039 cases were diagnosed with acute HAV infection from January 2013 to February 2018. Of these 1039 cases, 13.8% (144/1039) were Syrian refugees. In the whole group, 53% (546/1039) were males. The median age was 7.9 years, and Turkish cases were older than Syrian cases ($p<0.001$). When we analyzed the group according to years, Turkish patients were still older than Syrians. Hospitalization and admission to the intensive care rates were 49.4% (514/1039) and 0.3% (3/1039), respectively. There was no statistically significant difference between Turkish and Syrian cases regarding gender, hospitalization rate, and need for intensive care. The demographic features of the patients are shown in **Table 1**.

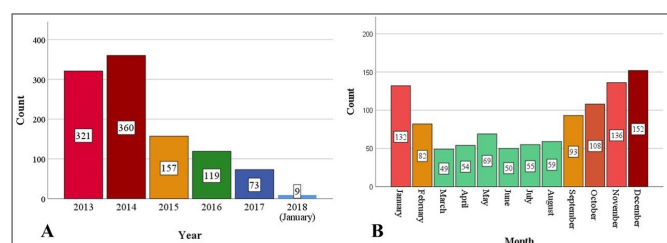
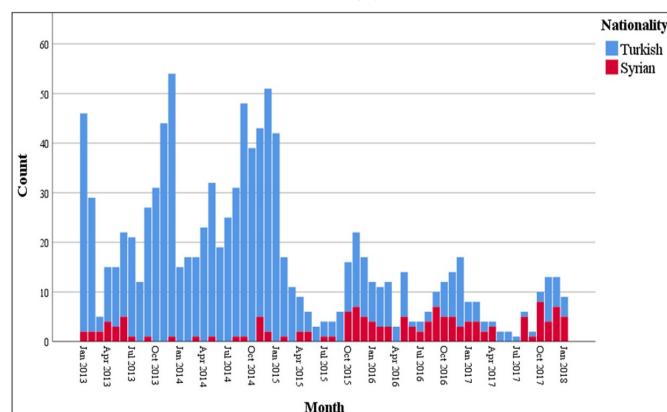
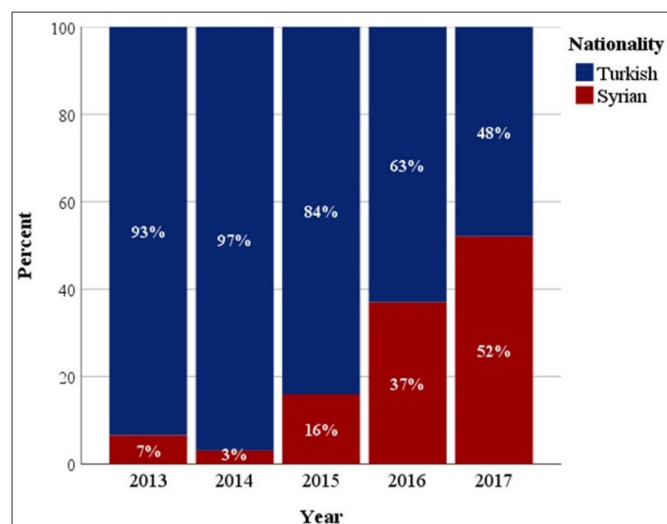
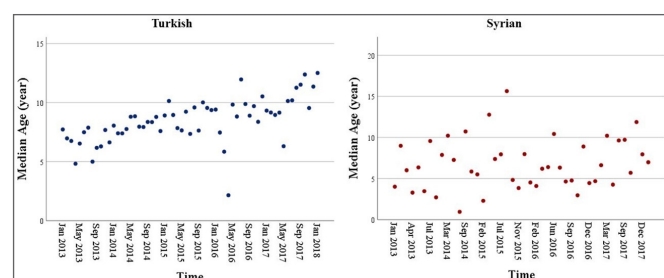
After 2013 and 2014, the number of cases tended to decrease. The months with the highest number of cases in the years were November, December, and January. The distribution of the cases by years and months are shown in **Figure 1**. While the total number of cases declined through the years, we saw the number of Syrian cases increase (**Figure 2**). The percentage of Syrian children in total cases in 2013 and 2017 was 6.5% and 52.1%, respectively (**Figure 3**). As a result, it is seen that the total number of cases has decreased over the years, but both the absolute number and the percentage of Syrian cases have increased over time. When we look at the change in age distribution according to years, while the average age of Turkish patients increased over the years, there was no significant change in the average age of Syrian cases (**Figure 4**).

In the hospitalized cases, the LOS was between 1 and 21 days with a median value of 4 days. ALT and AST median values were 1209 IU/L and 920 IU/L, respectively (**Table 1**). In the hospitalized population, Syrian cases had lower values of ALT and AST than the Turkish cases ($p<0.001$ and $p=0.02$, respectively). The average medical costs of hospitalization for HAV infection were \$246.8 per case.

Table 1. Demographic, clinical, and laboratory features of the HAV-infected cases

Variables	Total (n=1039)	Turkish cases (n=895)	Syrian cases (n=144)	p
Age, year median (min.-max.)	7.9 (0.7-17.1)	7.9 (1.4-17)	6.0 (0.7-16.2)	<0.001
2013 (n=321)	6.9 (0.7-17.1)	7 (1.6-17.1)	4.7 (0.7-14.1)	
2014 (n=360)	7.9 (1-16.7)	7.9 (1.4-16.7)	5.8 (1-11.8)	
2015 (n=157)	8.5 (1.5-15.9)	9.0 (1.6-15.9)	6.4 (1.5-15.6)	
2016 (n=119)	8.4 (1.1-16.2)	8.8 (1.5-16.2)	5.9 (1.1-15.4)	
2017 (n=73)	9.1 (1.2-16.2)	10.0 (1.6-15.9)	7.0 (1.2-16.2)	
Gender, male n (%)	546 (53)	463 (52)	83 (57)	0.40
Admission, n (%)				0.08
Inpatient	514 (49)	433 (48)	81 (56)	
Outpatient	525 (51)	462 (52)	63 (44)	
Need for intensive care, n (%)	3 (0.3)	2 (0.5)	1 (0.2)	0.40
In hospitalized patients (n=514)				
LOS, day median (min.-max.)	4 (1-21)	4 (1-21)	4 (1-16)	0.09
ALT IU/ml, median (min.-max.)	1209 (87-4113)	1305 (87-4113)	907 (98-2830)	<0.001
AST IU/ml, median (min.-max.)	920 (96-5111)	936 (96-5111)	535 (120-3302)	0.02

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; LOS, length of stay

**Figure 1.** Distribution of the cases by years (A) and months (B)**Figure 2.** Distribution of the cases by time and nationality**Figure 3.** Percentage of the cases by nationality**Figure 4.** Age distribution of the cases by time and nationality

DISCUSSION

Turkey has an intermediate level of anti-HAV seroprevalence, and HAV infection rates in Turkey have declined over the past 15 years (4,6,7). It should be noted that most children contract HAV infection asymptotically, so the actual number of infections can be predicted to be much higher than reported. There are many studies conducted at different times in Turkey on HAV seropositivity. Although it varies from region to region, the seroprevalence varies between 29.5% and 80% (8-10). Kurugol et al. (11) revealed that between 1998 and 2008, there was a shift in HAV seroprevalence from younger to older age groups and indicated that HAV infection in childhood was decreasing, and the pool of susceptible adolescents and young adults was increasing. In this study, it was observed that the age of disease acquisition in Turkish cases increased over time. On the other hand, there was no change in age during the study period among Syrian immigrants with a low vaccination rate.

Outbreaks have occurred in several refugee camps in Europe that are hosting refugees from Syria. A sharp rise in reported HAV cases was observed in Lebanon as early as 2013, concurrent with the Syrian crisis and influx of refugees (12). Köse et al. (13) found anti-HAV IgG seroprevalence at 47% in refugee children

in 2014. Between September 2015 and March 2016, parallel to peaking numbers of asylum seekers arriving in Germany, notified cases of hepatitis A in Germany increased substantially (14). In Greece, between April and December 2016, 177 laboratory-confirmed symptomatic cases were reported; 149 (84%) occurred in hosting camps, mostly among Syrian children under 15 years (15). In Turkey, the influx of refugees since 2011 has affected the outcomes of the current vaccination program due to the unvaccinated refugee population, possibly causing a suitable environment for epidemics such as viral hepatitis (16-18). Reporting rates of HAV infection by age group in the Syrian refugee population indicate that the seroprevalence of Syrian children may be lower than that reported in the literature. As we see in our study, the gradual increase in the percentage of immigrants over the years supports this argument. Seroprevalence data are needed for these age groups.

In this study, it was observed that approximately half of the cases with acute HAV infection were hospitalized. Although the LOS is short, it should not be forgotten that unnecessary hospitalization of the cases will also bring medical and economic problems. While making a decision for hospitalization, non-compliance with guidelines or not trusting home care can increase the hospitalization rates improperly. Additionally, the short time allotted to a patient in outpatient clinic conditions may cause insufficient evaluation of the case. Physicians may be inclined to hospitalize cases that they do not think are adequately evaluated in the outpatient clinic in order to be in the safe range. Among the admitted cases, a possible reason for the relatively lower AST and ALT values in Syrian cases may be that physicians tend to hospitalize these cases more for observation purposes.

After the implementation of the HAV vaccine in the national program, case numbers are declining. However, there are still susceptible individuals, especially Syrian refugees. In different studies, seropositivity for HAV is between 45-84% in immigrants, and in children, these ratios are decreasing (13,15,19). In Turkey, nearly 1,6 million Syrian children, and 10% of them are in Gaziantep (20). Prioritizing vaccination of this susceptible group started in the middle of 2017 in this region. We expect these infection rates to decrease in the future.

In this study, the average costs of a HAV infection-related hospitalization were \$246, while in the United States, in 2017, the average costs were \$16,232 (21). Cost-effective analyses performed in Ireland also showed that where HAV immunity is 45% or less, vaccination is the strategy of choice without a prior screening (22). When the average hospitalization costs are considered, the positive effect of national vaccination is much better understood. The time of being infected with HAV in Turkey is

shifting towards advanced ages, so vaccination should be supported in the pediatric population born before 2012 who were not routinely vaccinated against HAV.

There are several limitations in the study. Since the laboratory values of the outpatients were not evaluated, the disease severity of the outpatients and inpatients could not be compared. Indications for hospitalization of the cases are given by the physicians who see them. Although it was a single-center study, evaluating the criteria for the hospitalization decision was impossible. Comparisons of hospitalization rates among physicians could show the differences between physicians' patient management. Since there was no information about the vaccination status of the cases, no comment could be made on breakthrough infections or vaccination rates. Although it has limitations, this study demonstrated the epidemiological change of HAV infection over a long-term period of 5 years in a heavily populated city in Turkey.

CONCLUSION

Population changes due to mass migration movements have markedly affected the epidemiology of HAV infection. Implementing the HAV vaccine in the national vaccination program markedly reduced the possible negative effect of mass migration. However, due to the presence of susceptible individuals in the community, the provision of high vaccination rates remains essential. Continuous monitoring of epidemiological data and efforts to expand vaccine coverage are required for infection control. In order to prevent unnecessary hospitalizations in managing the cases, it is necessary to review the patient management of the physicians in the field.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Firat University Non-Interventional Clinical Research Ethics Committee (Date: 19.04.2018, Decision No: 08/16).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: No conflict of interest was declared by the author

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Author Contributions: The author declares that he has responsible for the design, execution, and analysis of the paper and that he has approved the final version.

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